

- [54] ANTIATHEROSCLEROTIC USE OF
KHELLIN AND KHELLININ
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[57] **ABSTRACT**

The present specification relates to the antiatheroscle-
rotic use of khellin and related furochromones, and
further provides novel antiatherogenic 6-halofurochro-
mones.

6 Claims, No Drawings

ANTIATHEROSCLEROTIC USE OF KHELLIN AND KHELLININ

DESCRIPTION

1. Technical Field

The present specification provides methods for use of pharmacologically active substances. Further the present specification provides novel compositions of matter and novel methods of their preparation.

The present specification particularly relates to the use of a known pharmacological agent, khellin, also known as "visamin", and structurally related antiatherogenic furochromones. Chemically, khellin is a furochromone. Furochromones are characterized generally by the structural formula I. Specifically, khellin is the furochromone of formula II, and is trivially named 7-methyl-4,9-dimethoxyfurochromone. Khellin and related furochromones are naturally occurring substances and have been used in crude form as pharmacological agents for centuries. Khellin is an extract from the plant *Ammi visnaga*. This plant grows wild in Eastern Mediterranean countries. Aside from khellin, *Ammi visnaga* is also a source of at least two other known and characterized furochromones, specifically visnagin (formula III) and khellinin (formula IV).

The formula III compound is trivially named 7-methyl-4-methoxyfurochromone and the formula IV compound is trivially named 7-glucyloxymethyl-4-methoxy-furochromone.

In *Ammi visnaga*, khellinin and khellin are ordinarily present in approximately equal amounts, while visnagin is present only as a minor or insignificant constituent. Moreover, khellinin has been reported to be of no therapeutic interest, notwithstanding the wide variety of known therapeutic uses for khellin. See, for example, Anrep, G. V. et al., "The Coronary Vasodilator Action of Khellin", in the *American Heart Journal* 37:531-542 (1949). Anrep, et al., also report the biological action of visnagin as being similar to that of khellin, but khellinin is somewhat less potent than khellin.

As indicated above, khellin exhibits a wide variety of pharmacological actions, rendering this compound a useful agent for numerous pharmacological purposes. For a comprehensive, but somewhat dated, review of the chemistry and physiological action of khellin-related products, see the reports of Hutterer, C. P., et al., *Chem. Revs.* 48:543-79 (1951) and Aubertin, E., *J. Med. Bordeaux* 127:819-23 (1950).

One principal action of khellin is its ability to induce relaxation of smooth muscle tissues. Particularly, khellin is known as a potent dilator of coronary blood vessels. This potent coronary vasodilator activity of khellin renders the compound useful in the treatment of angina pectoris and other diseases characterized by coronary artery insufficiency. For a description of the use of khellin in the treatment of such diseases, see Osher, H. L., et al., "Khellin in the Treatment of Angina Pectoris", *The New England Journal of Medicine* 244:315 (1951). Also the effects of enteric-coated khellin on coronary artery insufficiency is reported by Best, M. M., et al., *J. Med. Sci.* 222:35-9 (1951). The ability of khellin to relax smooth muscle also extends to gastrointestinal smooth muscle where khellin has been demonstrated to inhibit peristalsis, thus indicating antidiarrhetic potential. See Ramond-Hamet, *Compt. Rend.* 238:1624-6 (1954). Khellin may also be useful for the treatment of gastrointestinal disorders exhibiting a spas-

modic component, as suggested by Anrep, G. V., et al., cited above. Further the antispasmodic effects of khellin on the urethra is reported by Colombo, G., et al., *Arch. Sci. Med.* 97:71 (1954) and Montorsi, W., et al. *Presse Med.* 63:81 (1955).

The antispasmodic action of khellin also extends to bronchial smooth muscle, rendering khellin useful in the treatment of asthma and other hypoxic pulmonary diseases. In this regard, see Silber, E. N., et al., "The Effect of Khellin on Cardio-Pulmonary Function in Chronic Pulmonary Disease", published in 1951; Anrep, G. V., et al., "Therapeutic Uses of Khellin", *The Lancet*, Apr. 26, 1947, pages 557-8.

Khellin has also been reported to exert a hypotensive effect in humans by Jordan, H., *Arzneimittel-Forsch* 8:141-3 (1958), and 7:82-5 (1957). An additional account of the hypotensive effect of khellin is provided by Lian, C., et al., *Acta. Cardiol. (Brussels)* 5:373-88 (1950). With respect to overall cardiac effects, however, khellin has been reported to exert a cardiac depressive activity, while khellinin is reportedly a cardiac stimulant. In this regard see Samaan, K., et al., *J. Roy. Egypt Med. Assoc.* 33:953 (1950) and *J. Pharm. Pharmacol.* 1:538-44 (1949).

In addition to its effect on gastrointestinal smooth muscle reported above, khellin is also known as a gastric antisecretory and antiulcer agent. In this regard, the gastric antisecretory activity of khellin is reported by Hans, M. J., et al., *Compt. Rend. Soc. Biol.* 150:1820-1 (1956) and the antiulcer (gastric cytoprotective) properties of khellin are reported by LaBarre, J., et al., *Compt. Rend. Soc. Biol.* 150:1806-7 (1956) and 150:598-9 (1956).

Numerous other miscellaneous properties of khellin are also reported. For an account of its anthelmintic activity see Baytop, O. T., *Folia, Pharm. (Turkey)* 1:48-9 (1949). For an account of the CNS depressant activity of khellin see Chen, G., *Proc. Soc. Exptl. Biol. Med.* 78:306-7 (1951). For an account of the cytostatic activity of khellin see Apffel, C. A., *Deut. Med. Wochschr.* 80:414-16 (1955). Finally, the spermicidal action of khellin is reported by Swayne, V. R., et al., *Aman. J. Pharm.* 125:295-8 (1953).

Atherosclerosis in mammals is a disease characterized by the deposition of atherosclerotic plaque on arterial walls. While atherosclerosis exhibits many varied forms and consequences, typical consequences of atherosclerotic diseases include angina pectoris, myocardial infarction, stroke and transient cerebral ischemic attacks. Other forms of atherosclerotic diseases include certain peripheral vascular diseases and other ischemias (e.g., bowel and renal).

Medical science now recognizes that certain forms of atherosclerosis may be preventable or reversible. Agents capable of preventing or reversing atherosclerosis are characterized as exhibiting antiatherosclerotic activity. Since serum lipids have a recognized association with atherogenesis, an important class of antiatherosclerotic agents are those with serum lipid-modifying effects. Serum lipids implicated in atherogenesis include serum cholesterol, serum triglycerides, and serum lipoproteins.

With respect to serum lipoproteins, at least three different classes of these substances have been characterized: high density lipoproteins (HDL's), low density lipoproteins (LDL's), and very low density lipoproteins (VLDL's). HDL's are often referred to as alpha-lipo-

proteins, while LDL's and VLDL's are referred to as betalipoproteins. The enhancement to HDL levels (hyperalphalipoproteinemic activity) is postulated to have direct antiatherosclerotic effects. See Eaton, R. P., *J. Chron. Dis.* 31:131-135 (1978). In contrast, agents which reduce serum LDL's and serum VLDL's (hypobetalipoproteinemic agents) are also associated with antiatherogenic effects. See Haust, M.D., "Reaction Patterns of Intimal Mesenchyme to Injury and Repair in Atherosclerosis", *Adv. Exp. Med. Biol.* 43:35-57 (1974), which postulates that serum LDL is a factor in atherosclerotic lesion formation.

Numerous animal models have been developed for assessing antiatherogenic activity. Principal among these are models for assessing hypobetalipoproteinemic activity in the rat, antiatherosclerotic activity in the Japanese quail, and lipoprotein modifying activity in the monkey. For a description of the operation of the hypobetalipoproteinemic rat model, refer to the known methods of Schurr, P. E., et al., "High Volume Screening Procedure for Hypobetalipoproteinemia Activity in Rats" *Adv. Exp. Med. Biol.* 67: Atherosclerotic Drug Discovery, pp. 215-229, Plenum Press (1975). For a description of the Japanese quail model, see Day, C. E., et al., "Utility of a Selected Line (SEA) of the Japanese Quail (*Coturnic Coturnix japonica*) for the Discovery of New Anti-Atherosclerosis Drugs", *Laboratory Animal Science* 27:817-821 (1977).

A suitable primate model for assessing antiatherosclerotic activity of chemical compounds is found in the cynomolgus monkey. In these animals base-line values for VLDL's, LDL's, and HDL's can be determined by controlling diet over a period of several weeks and sampling plasma daily. After establishing control values, the effects of drug treatment are assessed by administering by gavage with a predetermined series of doses of test compounds for a similar period (e.g., two weeks).

4,9-Dimethoxyfurochromones are known in the art. Such known compounds include 7-ethyl, 7-phenyl, 7-propyl, and 7-ethoxycarbonyl analogs described by Shonberg, A., et al., *JACS* 72:1611-7 (1950); 7- γ -pyridyl analogs, described by Shonberg, A., *JACS* 77:5439 (1955); 7-furanyl analogs, described by Musante, C., et al., *Pharmaco. (Pavie) Ed. Sci.* 15:81-94 (1960); 7-carboxyaldehyde analogs, described by Mustafa, A., et al., *J. Org. Chem.* 26:886 (1961). Also, 6-substituted-4,9-dimethoxyfurochromones are known. See, for example, the compounds described by Hamed, Abu-Schad, *UAR J. Pharm. Sci.* 11:283 (1970).

2. Prior Art

Extensive pharmacological uses for khellin and related substances are known, as indicated above. Khellin analogs are also known in the art, as indicated above, particularly halofurochromone analogs. However, these halofurochromones are all 6-chloromethyl- or 6-iodomethyl furochromones. See Hamed, Abu-Shadz, *UAR J. Pharm. Sci.*, 11:283, 1970.

SUMMARY OF THE INVENTION

The present specification particularly provides:

(1) a method of treating or preventing atherogenic hyperlipoproteinemia in a mammal suffering from or susceptible to the development of an atherosclerotic disease which comprises:

administering systemically to said mammal an amount of a khellin-related product effective to significantly-reduce levels of atherogenic serum lipoproteins.

The present specification further provides:

(2) a method of reversing atherosclerotic lesions in a mammal which comprises:

administering systemically to said mammal an amount of khellin-related product effective to significantly reduce levels of atherogenic serum lipoproteins or selectively enhance levels of antiatherogenic serum lipoproteins.

A further aspect of the present disclosure comprises:

(3) a method of treating a mammal suffering from or susceptible to the development of an atherosclerotic disease which comprises:

administering systemically to said mammal an amount of khellin-related product effective to significantly reduce levels of atherogenic serum lipoproteins or enhance selectively levels of antiatherogenic serum lipoproteins.

Also disclosed herein is

(4) a method of treating or preventing atherogenic hypolipoproteinemia in a mammal suffering from or susceptible to the development of an atherosclerotic disease which comprises:

administering systemically to said mammal an amount of a khellin-related product effective to significantly enhance levels of antiatherogenic serum lipoproteins.

Moreover, the present specification further discloses:

(5) a 6-halofurochromone of formula V, wherein X is bromo, chloro or iodo; and wherein R₁ is:

- (a) hydrogen;
- (b) alkyl of one to 12 carbon atoms, inclusive;
- (c) alkoxyethyl of 2 to 8 carbon atoms, inclusive;
- (d) alkylthiomethyl of 2 to 8 carbon atoms, inclusive;
- (e) trifluoromethyl;
- (f) phenoxyethyl;
- (g) phenylthiomethyl;
- (h) phenoxyethyl or phenylthiomethyl substituted by chloro, fluoro, trifluoromethyl, alkyl of one to 3 carbon atoms, or alkoxy of one to 3 carbon atoms;
- (i) hydroxyethyl; or
- (j) cycloalkyl of 3 to 10 carbon atoms, inclusive.

Finally, there is provided in accordance with the present specification:

(6) a 6-halofurochromone intermediate of formula VI, VII, or VIII, wherein R₁' is:

- (a) isopropyl;
- (b) alkyl of 4 to 12 carbon atoms, inclusive;
- (c) alkoxyethyl of 2 to 8 carbon atoms, inclusive;
- (d) alkylthiomethyl of 2 to 8 carbon atoms, inclusive;
- (e) trifluoromethyl;
- (f) phenoxyethyl
- (g) phenylthiomethyl
- (h) phenoxyethyl or phenylthiomethyl substituted by chloro, fluoro, trifluoromethyl, alkyl of one to 3 carbon atoms, or alkoxy of one to 3 carbon atoms;
- (i) cycloalkyl of 3 to 10 carbon atoms, inclusive.

The novel 6-halofurochromones of formula V, at least some of the 6-halofurochromone intermediates of formula VIII, and the khellin-related products of *Ammi visnaga* are all characterized by pronounced antiatherogenic activity, rendering these compounds useful in the treatment and prophylaxis of atherosclerosis, atherogenic hyperlipoproteinemia (i.e., hypobetalipoproteinemia) and atherogenic hypolipoproteinemia (i.e., hypoalphalipoproteinemia), and the untoward consequences thereof. While these compounds exhibit this useful pharmacological activity in both mammalian and non-mammalian species, the use of these compounds in mammals, particularly humans, represents the intend-

ment of the disclosure herein. Those formula VIII intermediates characterized by antiatherogenic activity are readily determined by assessment of antiatherogenic potency in standard laboratory animals, such as are described above. Accordingly, formula VIII compounds with at least about one-tenth the antiatherogenic potency of khellin are useful for such purposes.

The mammals susceptible to the development of atherosclerotic diseases and the untoward consequences thereof are particularly those physically asymptomatic patients manifesting one or more risk factors known to predispose one to disease development. Such risk factors are high serum cholesterol and serum triglycerides, hypertension, obesity, diabetes, and genetic predisposition. Mammals manifesting two or more risk factors are deemed to be especially susceptible to atherosclerotic diseases. The khellin-related products and 6-bromofuranochromones all exhibit pronounced oral pharmacologic activity. Accordingly, in using these compounds for the instant purposes, an oral route of administration, either by conventional oral dosage forms or by mixture with food or feed, represents the preferred method of their systemic administration. Alternatively, however, these compounds may be administered by other convenient routes of administration whereby systemic activity is obtained. These other routes of administration would, accordingly, include rectal, vaginal, subcutaneous, intravenous, and like routes.

In humans, the preferred route of administration is oral, in the form of capsules or tablets containing khellin. Methods for the preparation of such oral dosage forms are known in the art. See, for example, the known formulations for khellin in the references hereinbefore described.

In order to obtain the instant pharmacologic activity of the antiatherogenic compounds in accordance with the instant specification, the patient or animal being treated must be given periodic doses of the khellin-related product or 6-halofuranochromone (or active 6-bromofuranochromone intermediate) in amounts effective to reduce atherogenic serum lipoproteins (e.g., betalipoproteins) or selectively enhance levels of antiatherogenic serum lipoproteins (e.g., enhancing alphalipoprotein levels, while suppressing, or at least unaffacting, betalipoprotein levels). Such effective dosages are readily determined by methods known in the art. For example, small daily doses of the khellin-related product or 6-halofurochromone (e.g., 50-100 mg) may be administered initially with higher succeeding doses until levels of atherogenic or antiatherogenic serum lipoproteins are favorably affected. By this regimen, a compound is administered initially at doses as low as about 50 mg per patient per day, with increasing doses up to about 200 mg per patient per day. In the event the antiatherogenic response in a patient being treated at a dose of 200 mg per day is insufficient, higher doses are also contemplated in accordance with the present disclosure, providing patient tolerance permits further increases in dose.

While the preferred dosage regimen is with single daily dosing of patients, also preferred for obtaining more uniform serum levels of khellin are multiple dosages per day (e.g., up to 4-6 times daily). Accordingly, when 4 daily doses of khellin are to be administered, each such dose may be about 50 mg per patient per dose (200-300 mg per patient per dose), or higher depending on tolerance.

Similar doses are employed in non-human mammals, e.g., 1-5 mg/kg/day.

The khellin-related products referred to above are the antiatherosclerotically active substances of *Ammi visnaga* and specifically include khellin and khellinin.

Finally, of the numerous 6-halofurochromone intermediates described above those exhibiting antiatherogenic effects in the rat, quail, and especially monkey represent useful antiatherogenic compounds in accordance with the present specification. Such activity is readily and routinely assessed and interpreted by those of ordinary skill in the art.

The novel compounds of the instant invention are all 6-halofurochromones by virtue of the substitution of halogen (chloro, bromo, or iodo) for hydrogen at the C-6 position of the skeletal structure for khellin. These 6-halofurochromones are also optionally substituted at the C-7 position by alkyl, alkoxymethyl, alkylthiomethyl, trifluoromethyl, phenoxyethyl, phenylthiomethyl, hydroxyalkyl, or cycloalkyl.

Examples of alkyl of one to 12 carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, and dodecyl, and isomeric forms thereof.

Examples of alkoxymethyl of 2 to 8 carbon atoms, inclusive, are methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, pentoxymethyl, hexoxymethyl, and heptoxymethyl, and isomeric forms thereof.

Examples of alkylthiomethyl are methylthiomethyl, ethylthiomethyl, propylthiomethyl, butylthiomethyl, pentylthiomethyl, hexylthiomethyl, and heptylthiomethyl.

Examples of cycloalkyl of 3 to 10 carbon atoms, inclusive, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclodecyl.

Among these various R_1 substituents, preferred compounds are those wherein R_1 is hydrogen, lower alkyl, (most especially methyl), methoxymethyl, methylthiomethyl, trifluoromethyl, phenoxyethyl, phenylthiomethyl, or hydroxymethyl. Of the above, most especially preferred are the compounds wherein R_1 is hydrogen or methyl.

The various novel 6-halofurochromones disclosed herein, including intermediates therefor, are all prepared by methods described in Charts A and B. With respect to these Charts, R_1 is as defined above, but is other than hydrogen or methyl. X is chloro, bromo, or iodo.

With respect to Chart A, the formula XXI compound, khellin is transformed to the formula XXII methylketone by hydrolysis under basic conditions. For example, aqueous potassium hydroxide at elevated temperatures is employed in this transformation in accordance with methods known in the art. See E. Spath and W. Gruber, *Chem. Ber.* 71:106 (1938).

Thereafter, the formula XXII benzofuranol is transformed to the formula XXIII β -diketone by a Claisen condensation with a carboxylic acid ester, wherein the carboxylic acid residue corresponds to the keto group being attached to the formula XXII product. Accordingly, there is employed in the preparation of the formula XXIII compound a carboxylic acid ester of the formula R_1COOR_2 , wherein R_2 is the ester residue (e.g., preferable a simple alkyl ester such as methyl or ethyl). The reaction proceeds conveniently in an organic solvent in the presence of sodium hydride, followed by treatment with alcoholic hydrochloric acid. Ordinarily, use of three or four equivalents of sodium hydride and

two to three equivalents of the carboxylic acid ester per equivalent of formula XXII starting material is preferred. Further, the reaction proceeds in the minimum amount of the organic solvent necessary to solubilize the reactants. Ordinarily, an aprotic polar solvent such as tetrahydrofuran is conveniently employed. However, in preparing the formula XXIII product wherein R_1 is other than a low molecular weight (sterically small) residue; the ester itself, R_1COOR_2 , is employed as the reaction diluent.

In the production of the formula XXIV compound, the formula XXIII intermediate therefor is ordinarily not isolated, but rather directly subjected to an acid-catalyzed cyclodehydration to yield the formula XXIV furochromone. This cyclodehydration ordinarily proceeds in the presence of a mineral acid in an organic solvent, such as an alkanol (e.g., hydrochloric acid in methanol). However, in preparing the formula XXIV compound where R_1 is trifluoromethyl, the chlorinated hydrocarbons (e.g., chloroform) represent preferred reaction diluents.

The formula XXV compound is then prepared from the formula XXIV compound by decyclization with pyrrolidine. The reaction proceeds in the presence of several equivalents of pyrrolidine per equivalent of formula XXIV compound at elevated temperature (e.g., refluxing methanol).

Optionally the formula XXIII compound is transformed directly to the formula XXV compound by methods and reagents employed in the above transformation of the formula XXIV compound to the formula XXV compound. This optional method is preferred only when R_1 is sterically bulky.

Thereafter, the formula XXVI halogenated product is recovered by first halogenation of the formula XXV compound by addition of the molecular halogen (e.g., bromine in chloroform), followed by hydrolysis to yield the formula XXVI 6-halofurochromone. With regard to the halogenation step, other conventional sources of halogen are alternatively employed, e.g., the positive halogen sources such as the hypochlorites. With regard to the latter reaction, the addition of water to the halogenated product effects the desired hydrolysis and cyclodehydration.

When R_1 in Chart A is methyl, the formula XXVI compound is prepared directly from the formula XXI compound via the formula XXV pyrrolidyl intermediate.

Chart B provides a method whereby the 6-halofurochromones disclosed herein wherein R_1 is hydrogen (i.e., the formula XXXIII compound) is prepared from the formula XXXI benzofuranol.

In accordance with Chart B the formula XXXI compound is treated with N,N-dimethylformamide dimethylacetal at elevated temperature to yield the formula XXXII enamino ketone. Thereafter, the formula XXXIII compound is prepared from the formula XXXII compound by the method described in Chart A for the preparation of the formula XXVI compound from the formula XXV compound.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preparation of the novel 6-halofurochromones of the instant specification is readily understood by the following examples:

EXAMPLE 1

6-Hydroxy-4,7-dimethoxy-5-benzofuranyl methyl ketone (Formula XXI compound of Chart A)

To a stirred solution of potassium hydroxide (193.2 g) in 1.5 l of water, heated to 75° C., is added 300 g of khellin (formula XXI) in 50 g portions over a period of 30 minutes. When khellin addition is complete, the resulting mixture is then heated to reflux for 2 hr and thereafter cooled to ambient temperature. Concentrated hydrochloric acid (300 ml) is then added to the cooled solution and the resulting precipitate is collected by filtration and dried at ambient temperature in a vacuum for 18 hr. The resulting crude yellow solid is then recrystallized from one liter of methanol, yielding 251 g of pure title product. Melting point is 99°-100° C. Silica gel TLC Rf is 0.60 in hexane and ethyl acetate (1:1). Infrared absorptions are observed at 3160, 3140, 2700, 1695, 1680, 1620, 1590, 1550, 1300, 1265, 1150, 1075, and 1060 cm^{-1} . NMR absorptions are observed at 7.52, 6.91, 4.15, 4.05, 2.72, and 13.06 δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 236, 221, 206, 203, 191, 175, 163, and 119. Carbon:hydrogen ratio is 60.65:5.15.

EXAMPLE 2

7-Methoxymethyl-4,9-dimethoxyfurochromone (Formula XXIV of Chart A: R_1 is methoxymethyl)

To sodium hydride (20.1 g of a 50% dispersion in oil) and tetrahydrofuran (20 ml freshly distilled from lithium aluminum hydride), combined under a nitrogen atmosphere to form a slurry, are added dropwise a mixture of the formula XXII product of Example 1 (20 g), methyl methoxyacetate (26.4 g) and dry tetrahydrofuran (50 ml). After the addition is complete (1.5 hr) the reaction mixture is then heated on a steam bath for 15 min and cooled to ambient temperature. Thereupon excess sodium hydride is destroyed by careful addition of ice and water (300 ml). Washing with diethyl ether (600 ml) yields an aqueous layer which is diluted with methanol (100 ml) and concentrated hydrochloric acid (75 ml). This mixture is then refluxed for 45 min and thereupon allowed to cool to ambient temperature. Upon extraction with methylene chloride (600 ml) the organic extracts were dried and concentrated under reduced pressure to yield a solid (26.2 g). Recrystallization from methanol yields 18.33 g of pure title product. Melting point is 116°-117° C. Silica gel TLC Rf is 0.57 in ethyl acetate. Infrared absorptions are observed at 3140, 3120, 1665, 1645, 1620, 1550, 1485, 1370, 1360, 1125, 1105, 1075, 1060, 855, and 870 cm^{-1} . NMR absorptions are observed at 7.66, 7.02, 6.30, 4.40, 4.21, 4.04, and 3.51 δ (deuteriochloroform). The mass spectrum exhibits peaks at 290, 275, 261, 246, 219, 201, and 287. The carbon:hydrogen ratio is 61.96:5.03.

Following the procedure of Example 2, but employing in place of methyl methoxyacetate corresponding methyl alkoxyacetates there are prepared the various formula XXIV 7-alkoxymethylfurochromones.

EXAMPLE 3

7-Methylthiomethyl-4,9-dimethoxyfurochromone (Formula XXIV of Chart A: R_1 is methylthiomethyl)

Following the procedure of Example 2, but employing ethyl 2-(methylthio)acetate, 56.5 g, in place of methyl methoxyacetate, there is prepared from the title

product of Example 1 (50 g) 47.0 g of pure title product as a tan solid. Melting point is 148°–150° C. Silica gel TLC Rf is 0.63 in ethyl acetate. Infrared absorptions are observed at 1650, 1625, 1545, 1480, 1380, 1125, 1070, 1060, 845, and 760 cm^{-1} . NMR absorptions are observed at 7.19, 7.05, 6.18, 4.2, 4.05, 3.60, and 2.25 δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 306, 291, 277, 259, 241, 231, 216, and 201. Carbon:hydrogen:sulphur ratio is 58.87:4.76:10.62.

Following the procedure of Example 3, but substituting the appropriate methyl or ethyl 2-(alkylthio)acetate in place of ethyl 2-(methyl)acetate, there are prepared the corresponding formula XXIV compounds wherein R_1' is alkylthiomethyl.

EXAMPLE 4

7-Phenylthiomethyl-4,9-dimethoxyfurochromone (Formula XXIV of Chart A: R_1 is phenylthiomethyl)

To a slurry of sodium hydride (32.44 g of a 50 percent dispersion in oil) and tetrahydrofuran (25 ml freshly distilled from lithium aluminum hydride) under a nitrogen atmosphere is added a mixture of the title product of Example 1 (40.0 g), methyl 2-(phenylthio)acetate (46.2 g) and tetrahydrofuran (75 ml). After addition is complete (1 hr) the resulting mixture is then cooled to ambient temperature and carefully quenched (sodium hydride destroyed) with water, 150 ml. The resulting mixture is then washed with diethyl ether (800 ml) and the resulting aqueous solution is diluted with methanol (300 ml) and concentrated hydrochloric acid (200 ml). After refluxing for 3 hr, the solution is then cooled to ambient temperature and extracted with methylene chloride, dried with sodium sulfate, and concentrated under reduced pressure to yield a brown solid. Dilution of this solid with methanol (100 ml) and filtration yields 31.57 g of pure title product. Melting point is 132°–134° C. Silica gel TLC Rf is 0.46 in hexane and ethyl acetate (1:3). Infrared absorptions are observed at 3140, 3120, 1690, 1620, 1590, 1545, 1485, 1385, 1365, 1345, 1210, 1025, 1070, 1055, and 1035 cm^{-1} . NMR absorptions are observed at 7.18, 7.20–7.55, 7.0, 6.08, 4.15, 4.05, and 3.98 δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 368, 260, 259, 258, 231, and 216. Carbon:hydrogen:sulphur ratio is 64.98:4.24:8.56.

Following the procedure of Example 4, but employing the appropriate methyl 2-phenyl(thio)alkylacetate in place of methyl 2-(phenylthio)acetate, there are prepared the corresponding formula XXIV products wherein R_1' is phenylthiomethyl.

EXAMPLE 5

7-Isopropyl-4,9-dimethoxyfurochromone (formula XXIV of Chart A (R_1 is isopropyl)).

To a mixture of the title product of Example 1 (50 g) and methyl 2-methylpropionate (300 ml) under a nitrogen atmosphere is added sodium hydride (40 g as a 50% oil dispersion) over a period of 25 min. When evolution of hydrogen gas ceases, the reaction mixture is then heated at reflux for 22 hr and thereafter cooled to ambient temperature. Quenching (destroying sodium hydride) with water and diluting with diethyl ether yields a 2-phase system from which the aqueous phase is separated and washed with diethyl ether (200 ml). The aqueous phase is then acidified with 25% aqueous hydrochloric acid and extracted with diethyl ether (400 ml). The combined ethereal extracts are then dried over magnesium sulfate and concentrated under reduced pressure to yield a light brown oil. The oil is then di-

luted with methanol (300 ml) and anhydrous hydrochloric acid, which is bubbled through the methanolic solution. The methanolic solution is then refluxed for 2 hr, cooled to ambient temperature, diluted with water (200 ml), and extracted with methylene chloride (400 ml). The combined organic extracts are then dried over magnesium sulfate and concentrated under reduced pressure to yield a light tan oil which is recrystallized from ethyl acetate and hexane, yield 34.3 g of essentially pure title product. Melting point is 116°–118° C.

Chromatographing a 16.0 g sample of the essentially pure product on 1.35 kg of silica gel packed in hexane and ethyl acetate (1:1) and eluting with this solvent yields 13.98 g of pure title product. Silica gel TLC Rf is 0.66 in hexane and ethyl acetate (1:1). Infrared absorptions are observed at 3130, 3100, 1650, 1625, 1595, 1540, 1480, and 1075 cm^{-1} . NMR absorptions are observed at 7.64, 7.0, 6.07, 4.15, 4.01, 2.90, and 1.31 δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 288, 273, 259, 245, 244, 217, 215, and 177. The carbon:hydrogen ratio is 66.73:5.52.

Following the procedure of Example 5, but employing the appropriate methyl alkanoate in place of methyl 2-methylpropionate, there are obtained the corresponding formula XXIV compounds wherein R_1' is alkyl.

EXAMPLE 6

7-Cyclopropyl-4,9-dimethoxyfurochromone (Formula XXIV of Chart A: R_1 is cyclopropyl).

Following the procedure of Example 5, employing methyl cyclopropanecarboxylate (75 g) in place of methyl 2-methylpropionate, the title product of Example 1 (15 g) is transformed to 8.60 g of pure crystalline title product. Melting point is 135°–137° C. Silica gel TLC Rf is 0.55 in hexane and ethyl acetate (1:1). Characteristic infrared absorptions are observed at 3130, 3100, 1650, 1625, 1595, 1540, and 1480 cm^{-1} . NMR absorptions are observed at 7.62, 7.0, 6.1, 4.13, 4.02, 1.7–2.11, and 0.98–1.28 δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 286, 271, 237, 243, 215, 205, 177, 149, and 147. Carbon:hydrogen ratio is 67.00:4.86.

Following the procedure of Example 6, but employing the appropriate methyl cycloalkanecarboxylate in place of methyl cyclopropanecarboxylate, there are prepared the corresponding formula XXIV compounds wherein R_1' is cycloalkyl.

EXAMPLE 7

7-Undecyl-4,9-dimethoxyfurochromone (Formula XXIV of Chart A: R_1 is n-undecyl)

To a mixture of the title product of Example 1 (60 g.) and ethyl laurate (500 g) under nitrogen atmosphere is added sodium hydride (45 g in a 50% oil dispersion) over a period of 30 min. After addition of sodium hydride is complete, the reaction mixture is heated to 80° C. for 1.5 hr and thereafter cooled to ambient temperature. After solidification of a light brown mass, water (dropwise) and diethyl ether (500 ml) is employed to quench the reaction mixture. Thereafter additional water (for a total of 200 ml) is carefully added and the aqueous layer separated. The aqueous layer is then washed with diethyl ether and thereafter diluted with chloroform (300 ml) and acidified with 25% aqueous hydrochloric acid. The chloroform layer is then separated and the aqueous layer extracted with chloroform

(100 ml) and the combined organic phase is then dried and filtered. After drying, anhydrous hydrochloric acid is passed through the chloroform solution for several minutes and the solution is refluxed for one hr. After cooling to ambient temperature the chloroform is then removed under reduced pressure yielding a brown oil (95.32 g) which solidifies.

Chromatographing of a 5 g sample of the oil on 250 g on silica gel packed with ethyl acetate and hexane (1:1) yields 2.36 g of pure title product. Melting point is 78°–79° C. Silica gel TLC Rf is 0.73 in hexane and ethyl acetate (1:1). Infrared absorptions are observed at 3120, 3060, 1660, 1620, 1555, 1485, 1375, 1360, 1125, 1095, 845, 765, and 720 cm⁻¹. NMR absorptions are observed at 7.65, 7.03, 6.1, 4.2, 4.08, 2.65, 1.05–1.90 and 0.87δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 400, 386, 385, 371, 357, 329, 315, 229, 177, 105, 43, and 41. The carbon:hydrogen ratio is 71.88:8.17.

Following the procedure of Example 7, but employing the appropriate ethyl alkanoate in place of ethyl laurate, there are prepared each of the corresponding formula XXIV products wherein R₁' is alkyl.

EXAMPLE 8

7-Trifluoromethyl-4,9-dimethoxyfurochromone (Formula XXIV of Chart A: R₁ is trifluoromethyl)

To sodium hydride (40.51 g of a 50% dispersion in oil) is added a mixture of the title product of Example 1 (50 g) and ethyl trifluoroacetate (90 g) under a nitrogen atmosphere. After addition is complete, the resulting mixture is stirred an additional 30 min at ambient temperature. Thereafter the reaction mixture is carefully quenched with water (200 ml), followed by addition of diethyl ether (500 ml). The aqueous phase is then separated and washed with diethyl ether (500 ml), diluted with chloroform, and acidified with 10% aqueous hydrochloric acid. The chloroform layer is then separated, and the aqueous layer extracted with chloroform (100 ml). The combined organic phases are then dried with magnesium sulfate and filtered. Anhydrous hydrochloric acid is then passed into the chloroform solution for several minutes, followed by refluxing for 45 min. The resulting mixture is then allowed to cool at ambient temperature and the solvent removed under reduced pressure, yielding a dark brown solid. After washing with diethyl ether (200 ml), there is obtained 35.26 g of pure title product. Recrystallization from ethyl acetate in hexane yields a product with melting point 166°–168° C. Silica gel TLC Rf is 0.57 in 5% ethyl acetate in chloroform. Infrared absorptions are observed at 3130, 1665, 1650, 1615, 1550, 1480, 1270, 1215, 1185, 1145, 1135, 1070, 950, and 870 cm⁻¹. NMR absorptions are observed at 7.69, 7.05, 6.60, 4.21, and 4.03δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 314, 299, 285, 271, 270, 243, 215, 200, 120, and 105. The carbon:hydrogen:fluorine ratio is 53.77:2.92:18.08.

Following the procedure of Examples 2–8, each of the various formula XXIV compounds of Chart A is prepared from the title product of Example 1 and the appropriate carboxylic acid ester.

EXAMPLE 9

1-(6-Hydroxy-4,7-dimethoxy-benzofuranyl)-3-(1-pyrrolidinyl)-2-buten-1-one (Formula XXV of Chart A: R₁ is methyl)

A methanolic solution of khellin (5.2 g) and pyrrolidine (2.82 g) is heated at 80° C. for 6 hr. Upon cooling,

bright orange crystals precipitate from the reaction mixture. After filtration, there is obtained 6.3 g of pure title product. Silica gel TLC Rf is 0.74 in ethyl acetate. Infrared absorptions are observed at 3180, 3160, 3120, 2300, 1630, 1600, 1530, 1345, 1325, 1260, 1170, 1155, 1140, 1130, 1060, 1050, and 1030 cm⁻¹. NMR absorptions are observed at 7.45, 6.8, 6.25, 4.05, 3.89, 3.22–3.70, 2.68, and 1.8–2.15δ. The mass spectrum exhibits peaks at 331, 300, 261, 220, 205, 177, 111, 110, 83, and 70. The carbon:hydrogen:nitrogen ratio is 65.09:6.32:4.18.

Following the procedure of Example 10, but employing each of the various formula XXIV 4,9-dimethoxy-7-substituted furochromones, there are prepared each of the various corresponding formula XXV products.

EXAMPLE 10

6-Bromo-7-methyl-4,9-dimethoxyfurochromone (Formula XXVI of Chart A: R₁ is methyl)

To a chloroform (20 ml) solution of the title product of Example 9 (1.10 g) at 0° C. is added dropwise a chloroform (5 ml) solution of bromine (528 mg). After the addition of bromine is complete, the reaction mixture is diluted with water (50 ml) and stirred vigorously for 5 min. The chloroform layer is then separated and the aqueous layer extracted with chloroform (15 ml). The combined organic extracts are then dried over sodium sulfate and concentrated under reduced pressure to yield 1.2 g of a dark green material. This material is then chromatographed on 50 g of silica gel packed and eluted with 10% ethyl acetate and chloroform. Fractions containing pure title product (480 mg) are combined. Melting point is 176°–177° C. Silica gel TLC Rf is 0.70 in ethyl acetate. Infrared absorptions are observed at 3120, 1650, 1640, 1625, 1610, 1590, 1550, 1540, 1480, 1350, 1330, 1265, 1070, 1050, 870, 785, and 770 cm⁻¹. NMR absorptions are observed at 7.65, 7.01, 4.2, 4.04, and 2.65δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 340, 338, 325, 323, 297, 296, 295, 294, 279, 277, 250, 177, and 175. The carbon:hydrogen:bromine ratio is 49.74:3.36:23.57.

Following the procedure of Example 5, but employing in place of the title product of Example 9, each of the various corresponding formula XXV compounds described following Example 9, there are prepared each of the corresponding formula XXVI 6-bromofurochromones in accordance with the instant specification.

Further following the above procedures but employing the appropriate halogen other than bromine, there are prepared the various formula XXVI 6-chlorofuranochromones or 6-iodofuranochromones in accordance with the instant specification.

EXAMPLE 11

6-Bromo-4,9-dimethoxyfurochromone (Formula XXXIII of Chart B)

A. 1-(6-Hydroxy-4,7-dimethoxy-5-benzofuranyl)-3-dimethylamino-2-propen-1-one. The title product of Example 1 (25 g) and N,N-dimethylformamide dimethylacetal (13.7 g) are heated in an oil bath for 2.5 hr. The reaction product then precipitates and is cooled to ambient temperature. Excess methanol is then removed under reduced pressure and the resulting solid crystallized from methanol to yield 23.2 g of product. Melting point is 137°–139° C. Silica gel TLC Rf is 0.12 in hexane and ethyl acetate (1:1). Infrared absorptions are observed at 1625, 1555, 1535, 1500, 1265, 1060, 875, 770,

and 730 cm^{-1} . NMR absorptions are observed at 8.00, 7.47, 6.82, 6.30, 4.05, 3.90, and 2.8–3.31 δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 291, 221, 220, 206, 205, 177, 163, and 98. Carbon:hydrogen:nitrogen ratio is 61.65:6.12:4.90.

B. 6-Bromo-4,9-dimethoxyfurochromone. To a chloroform (20 ml) solution of the reaction product of Part A (1.0 g) is added dropwise a chloroform (7 ml) solution of bromine (549 mg). After the bromine discolors, the reaction mixture is diluted with water (50 ml) and vigorously stirred for 5 min. Thereafter the chloroform layer is separated and the aqueous layer extracted with chloroform (50 ml). The combined chloroform extracts are then dried over sodium sulfate and concentrated under reduced pressure to yield a light yellow oil (825 mg). Chromatographing on 60 g of silica gel packed and eluted with 10% ethyl acetate in chloroform yields 640 mg of pure title product. Melting point is 166° – 167° C. Silica gel TLC R_f is 0.60 in 10% ethyl acetate and chloroform. Infrared absorptions are observed at 3150, 3120, 2080, 1660, 1615, 1590, 1550, 1480, 1350, 1310, 1225, 1145, 1070, 1040, and 770 cm^{-1} . NMR absorptions are observed at 8.22, 7.71, 7.06, 4.28, and 4.11 δ . The mass spectrum exhibits peaks at 326, 324, 311, 309, 297, 295, 284, 282, 281, 280, and 53. Carbon:hydrogen:bromine ratio is 43.22:2.70:24.57.

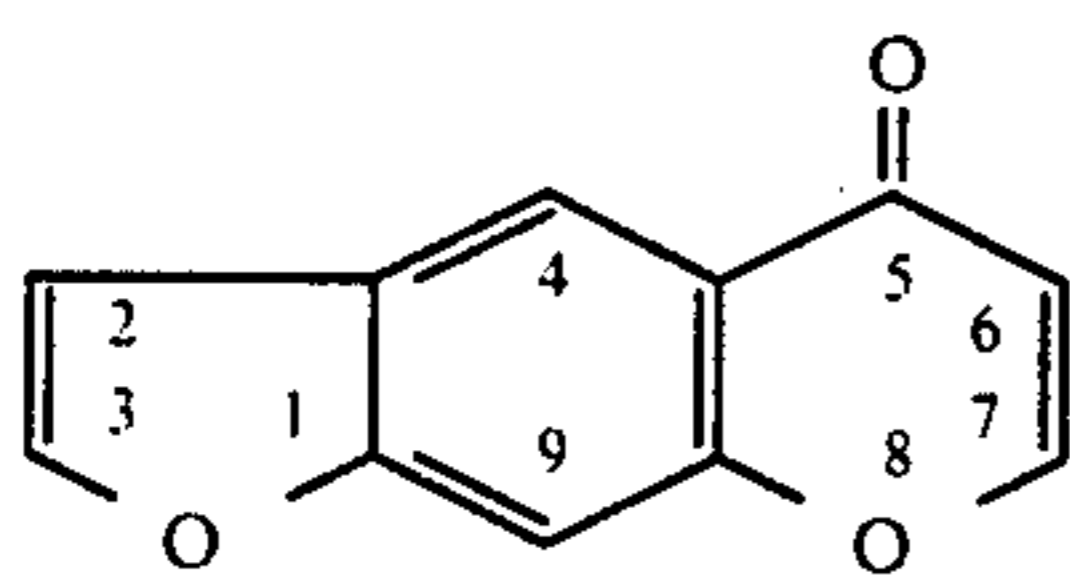
Following the procedure of Example 11, but employing the appropriate halogen other than bromine, there are prepared the various formula XXXIII compounds where X is chloro or iodo.

EXAMPLE 12

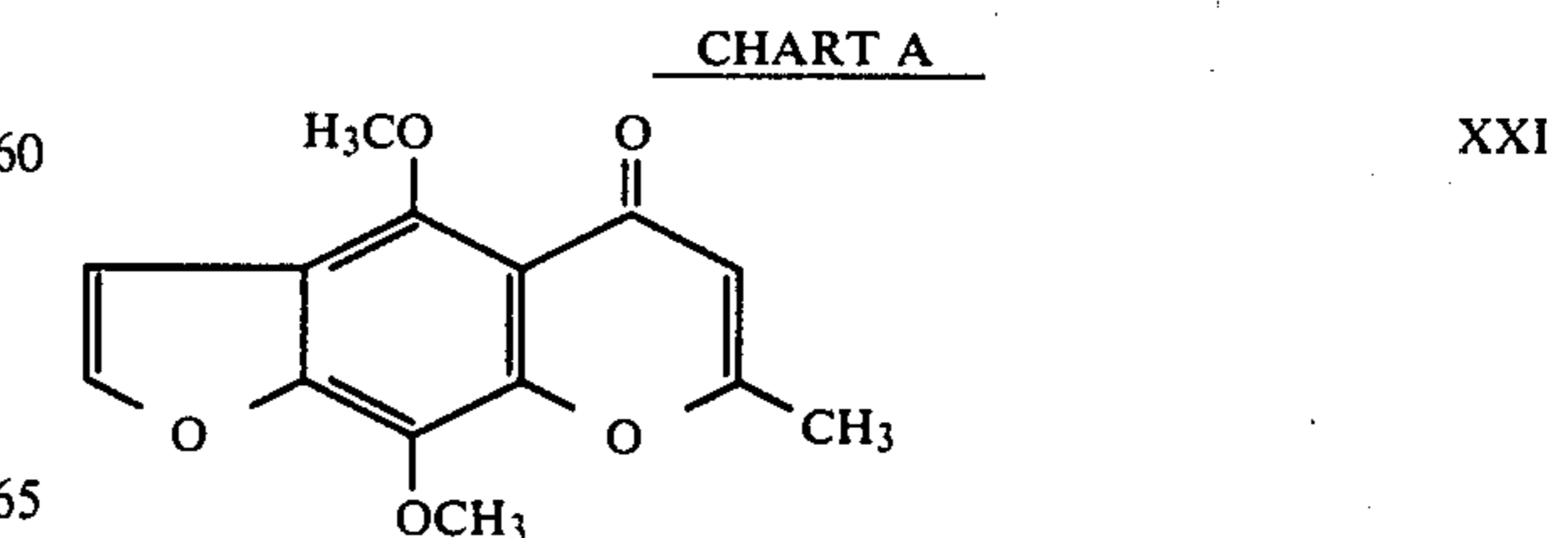
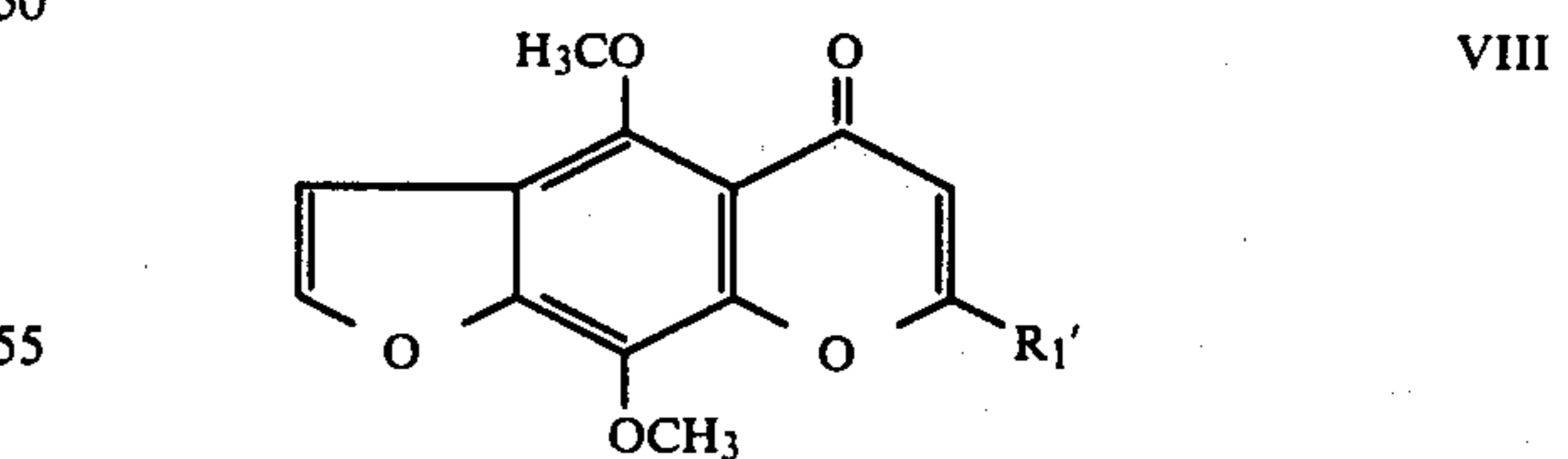
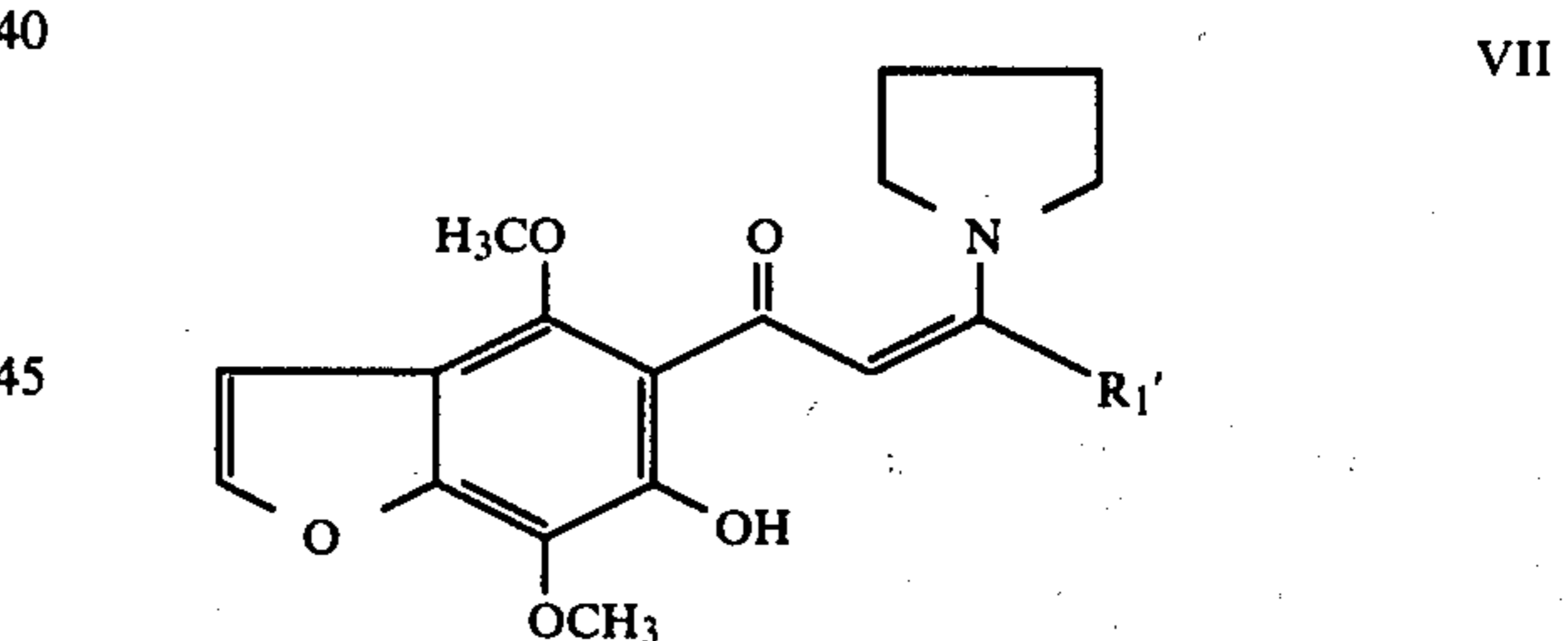
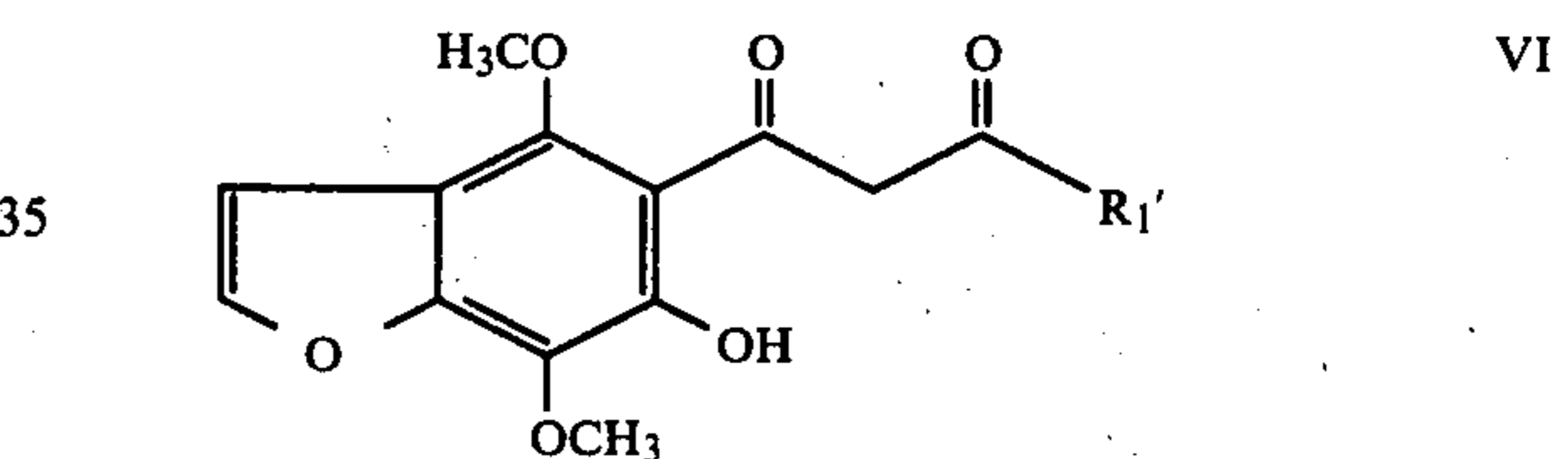
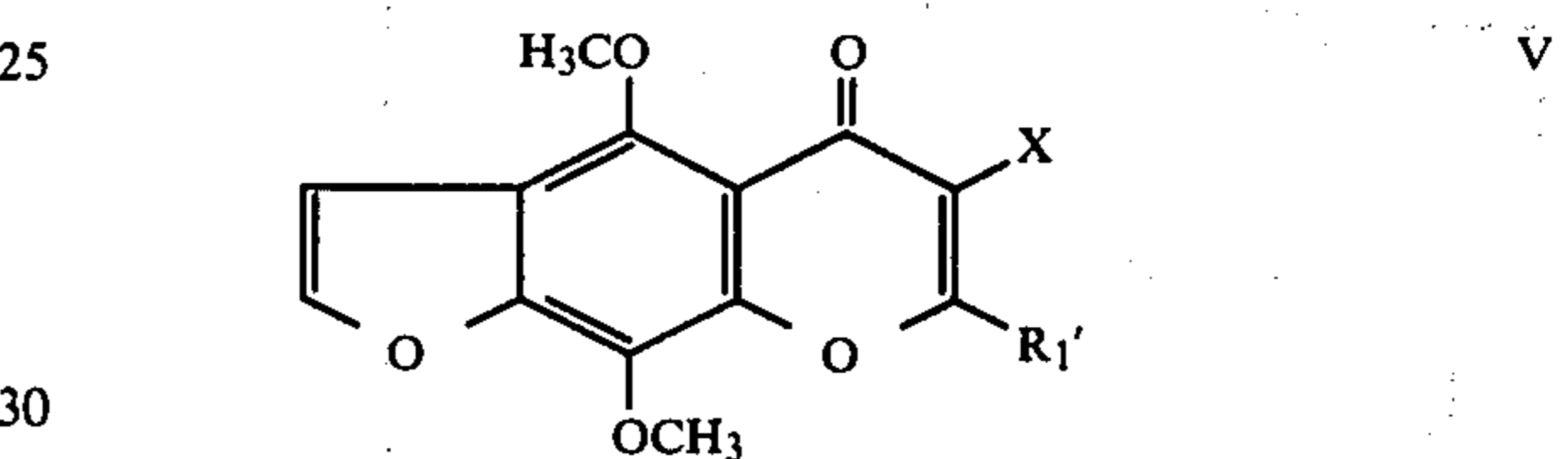
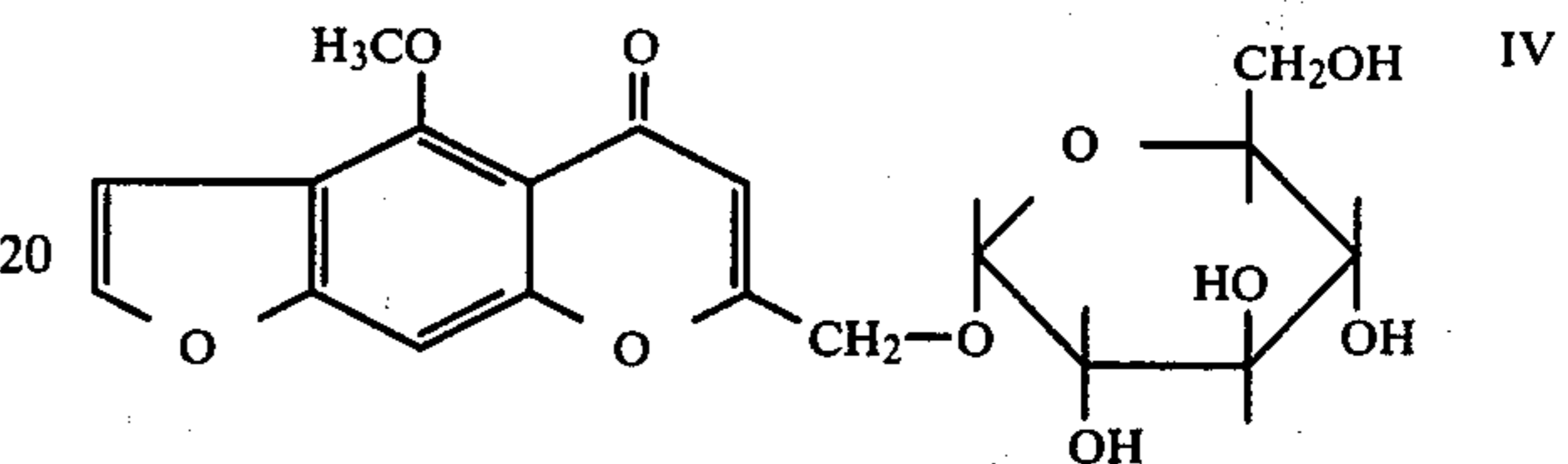
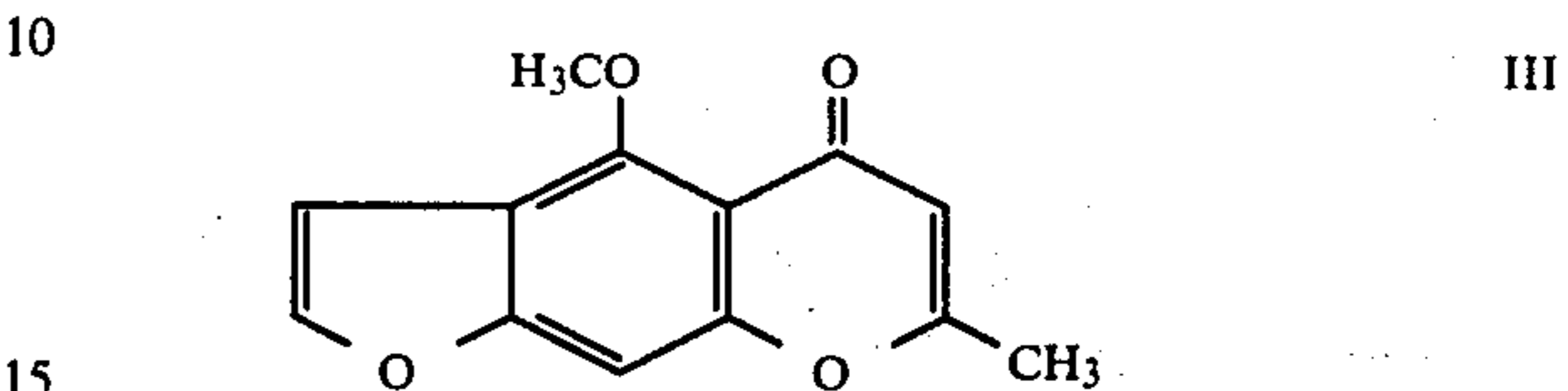
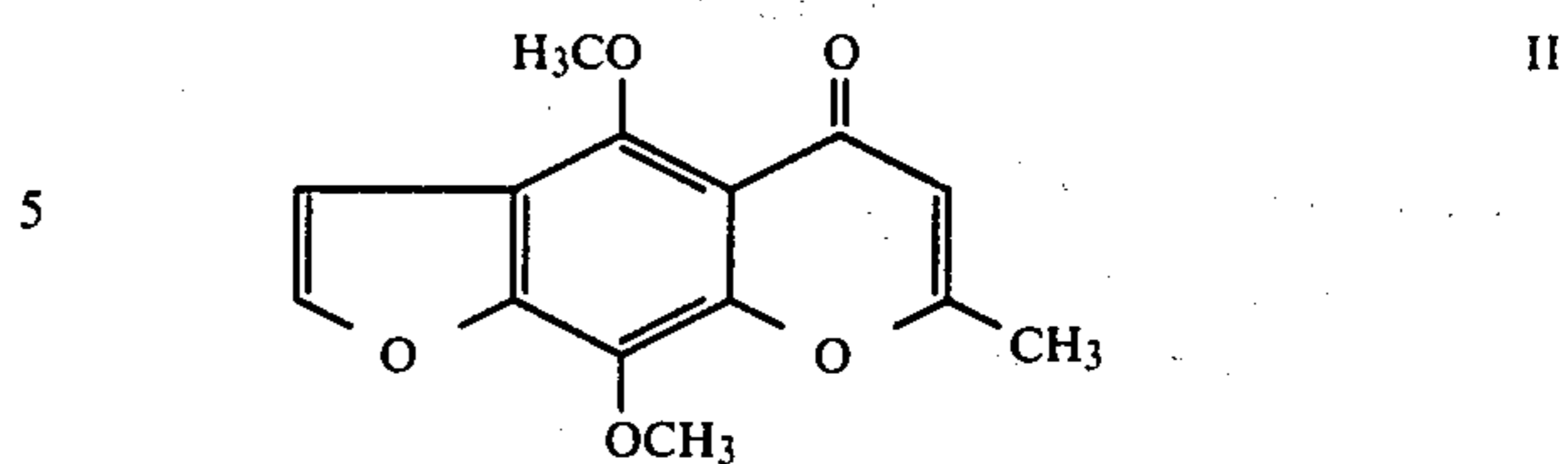
6-Chloro-4,9-dimethoxyfurochromone (Formula XXXIII of Chart B)

The reaction product of Example 11, part A (5.0 g) in chloroform (100 ml) is cooled to 0° C. and treated dropwise with a chloroform solution of t-butyl hypochlorite (1.85 g in 10 ml of chloroform) over 3 minutes with vigorous stirring. Thereafter, anhydrous hydrochloride is bubbled through the solution causing the reaction mixture to become a dark brown color. After stirring for an additional 2.5 hr, water, (58 ml) is added and stirring is continued for an additional 45 min. Thereafter the organic layer is separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to yield 3.83 g of a dark brown solid. Successive recrystallizations from methanol yield 1.75 g of pure title product. Melting point is 178° – 179° C. Silica gel TLC R_f is 0.57 in ethyl acetate and chloroform (1:9). Infrared absorptions are observed at 3150, 3120, 1660, 1615, 1590, 1550, 1480, 1350, 1310, 1145, 1070, 1040, and 770 cm^{-1} . NMR absorptions are observed at 8.1, 7.65, 7.02, 4.20, and 4.02 δ (deuteriochloroform solvent). The mass spectrum exhibits peaks at 282, 280, 267, 265, 251, 247, 246, 222, 209, 181, 177. Carbon:hydrogen:chlorine ratio is 55.64:3.41:12.52.

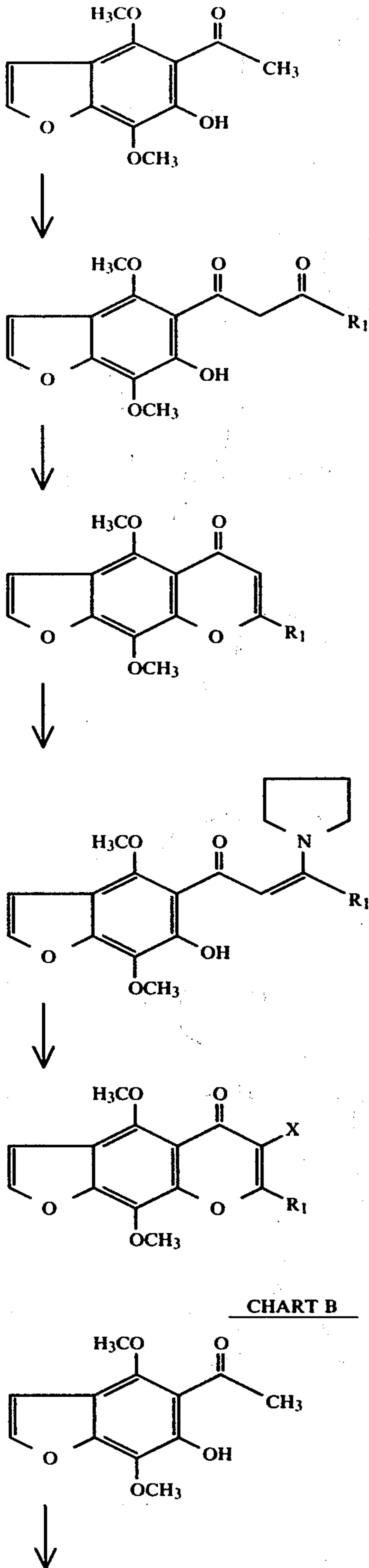
FORMULAS



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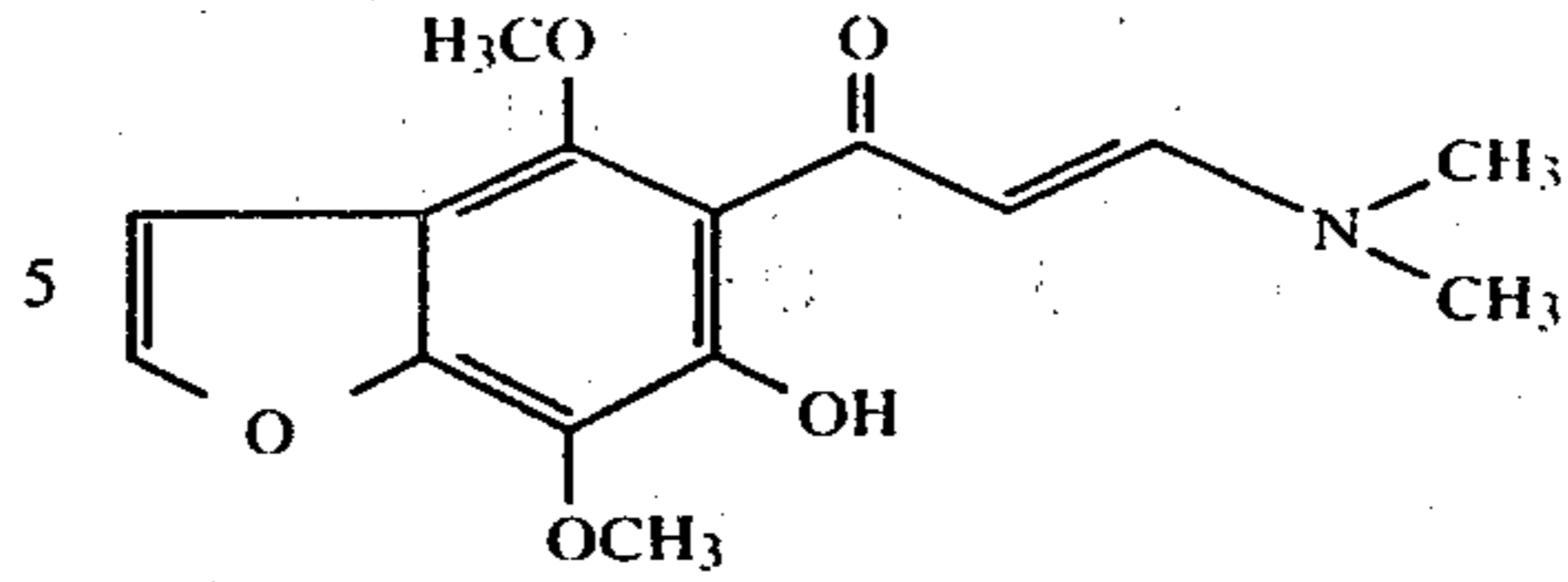


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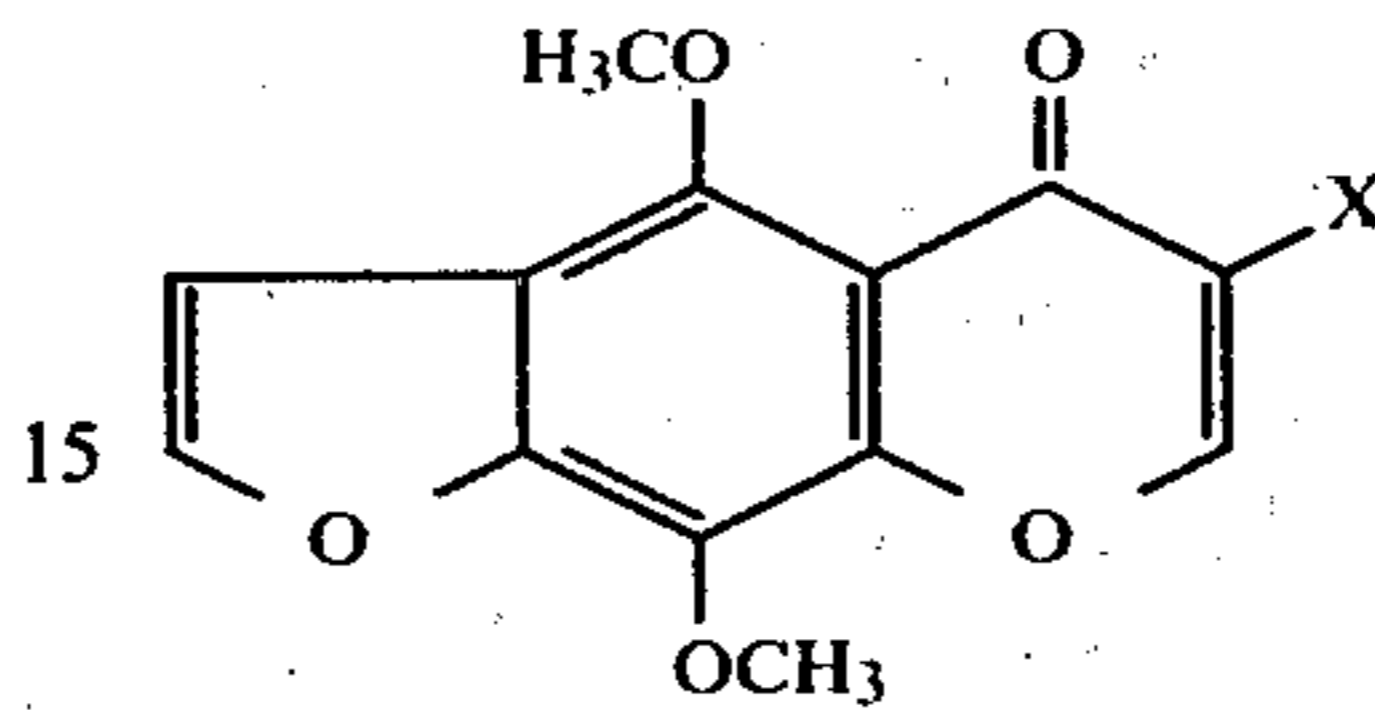
XXII



XXXII

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XXIII



XXXIII

We claim:

- 20 1. A method of treating or preventing serum lipid associated atherogenic hyperbetalipoproteinemia in a human suffering from or susceptible to the development of an atherosclerotic disease which comprises:
 - 25 administering systemically to said human an amount of khellin or khellinin effective to significantly reduce levels of atherogenic serum betalipoproteins.
 - 30 2. A method of reversing serum lipid associated atherosclerotic lesions in a human which comprises:
 - 35 administering systemically to said human an amount of khellin or khellinin effective to significantly reduce levels of atherogenic serum betalipoproteins.
 - 40 3. A method of reversing serum lipid associated atherosclerotic lesions in a human which comprises:
 - 45 administering systemically to said human an amount of khellin or khellinin effective to selectively enhance levels of antiatherogenic serum alphasalipoproteins.
 - 50 4. A method of treating a human suffering from or susceptible to the development of a serum lipid associated atherosclerotic disease which comprises:
 - 55 administering systemically to said human an amount of khellin or khellinin effective to significantly reduce levels of atherogenic serum betalipoproteins.
 - 60 5. A method of treating a human suffering from or susceptible to the development of a serum lipid associated atherosclerotic disease which comprises:
 - 65 administering systemically to said human an amount of khellin or khellinin effective to selectively enhance levels of antiatherogenic serum alphasalipoproteins.
 - 66 6. A method of treating or preventing serum lipid associated atherogenic hypoalphalipoproteinemia in a human suffering from or susceptible to the development of an atherosclerotic disease which comprises:
 - 70 administering systemically to said human an amount of khellin or khellinin effective to significantly enhance levels of antiatherogenic serum alphasalipoproteins.
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